Dose-response effects of exercise on bone mineral density and content in postmenopausal women

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Abstract:

Exercise is one of the most widely used non-pharmacological strategies to prevent bone resorption during menopause. Given the detrimental consequences of bone demineralization, the purpose of this study was to examine the effects of prescribing different exercise volumes on bone mineral density and content in previously inactive, post-menopausal women during a 12-month intervention and 1 year after intervention completion. Four hundred post-menopausal women were randomized to either 150 min/wk (MODERATE dose group) or 300 min/wk (HIGH dose group) of aerobic exercise. Total bone mineral density (g/cm^2) and bone mineral content (g) were assessed at baseline, 12 months (end of the intervention) and 24 months (follow-up) using whole body dual-energy X-ray absorptiometry. At 12 months, mean bone mineral density among women in the HIGH dose group was estimated to be 0.006 g/cm^2 (95% CI: 0.001-0.010; $P = 0.02$) higher than that of women randomized to the MODERATE dose group. At 24 months, the mean difference between groups remained statistically significant, indicating higher mean bone mineral density among women in the HIGH dose group (0.007 g/cm^2; 0.001-0.001; $P = 0.04$). No significant differences between groups were found at any time point for bone mineral content. In an exploratory analysis, women who completed more min/wk of impact exercises had significantly higher mean levels of bone mineral density at 12 months compared to baseline (0.006 g/cm^2, 95% CI: 0.006-0.012; $P = 0.03$). These findings suggest that higher volumes of exercise, especially impact exercise, lead to a smaller decline in total bone mineral density, which may remain following intervention completion.

Keywords: exercise volume | menopause | osteopenia | osteoporosis

Article:

1 INTRODUCTION

Menopause accelerates bone loss as a result of decreased estrogen production.[1] Osteopenia and osteoporosis are conditions characterized by low bone mineral density and bone mineral content, with a heightened fracture risk.[2, 3] Affecting approximately one in three women, post-menopausal osteoporosis is a highly prevalent condition and the incidence is expected to increase in the upcoming years.[4] Osteoporosis-related fractures are associated with a high risk of mortality and morbidity in post-menopausal women.[5] Preventing the long-term loss of bone in post-menopausal women is therefore a major public health priority given its prevalence and impact on physical functionality.

Several lifestyle and pharmacologic interventions to prevent the loss of bone mineral density in women have been assessed within randomized settings.[6] Pharmacological treatments, such as the prescription of bone resorption inhibitors or bone formation stimulators, are widely used in post-menopausal osteoporosis to help maintain bone mineral density.[7] However, the widespread and long-term use of these drugs is limited because of possible side effects (eg, fever, nausea, muscle and bone pain, toxicity, heart disease, and cancer).[8]

Exercise is one of the most widely used non-pharmacological strategies to prevent bone resorption.[9] It is generally acknowledged that regular exercise can positively influence bone metabolism.[10] Bone is an adaptive tissue, and one of the mechanisms whereby exercise can improve bone strength is by increasing muscle mass because of the mechanical load that it exerts on the skeleton.[11] Studies have shown that the osteogenic effects of exercise are associated with activities that induce high muscle tension, such as resistance training,[12] and high impact loading activities, such as jumping.[13] However, findings in post-menopausal women have been inconsistent thus far, with some studies observing improvements in bone mineral density after an exercise program,[14] while others reported no effects.[15, 16] Given the detrimental consequences of bone demineralization during menopause, further research is needed to determine the optimal dose of exercise that is needed to prevent post-menopausal bone loss.[17]

The purpose of the present study was to assess the effects of prescribing different volumes of aerobic exercise on total bone mineral density and bone mineral content changes in previously inactive post-menopausal women during a year-long intervention and 1 year later. We hypothesized that women randomized to a higher dose of aerobic exercise would have a slower age-related decline in bone mineral density and content compared to women randomized to a lower dose of aerobic exercise. We also hypothesized that women who voluntarily choose to spend more time doing impact activities (eg, running, rope skipping, and walking) instead of non-impact activities (eg, cycling, rowing, and swimming) would experience the least amount of decline in bone mineral density.

2 METHODS

2.1 Study design and participants

The study design and methods for the Breast Cancer and Exercise Trial in Alberta (BETA) are described in more details elsewhere.[18] This study was a two-center, two-arm, 12-month

randomized controlled trial conducted in Calgary and Edmonton, Alberta, Canada. A total of 400 English-speaking, post-menopausal women aged 50-74 years who resided in either Calgary or Edmonton were recruited and randomized to either 150 min/wk (MODERATE) or 300 min/wk (HIGH) of aerobic exercise. Additional inclusion criteria included the following: being recreationally inactive (< 90 min/wk of exercise or if between 90 and 120 min/wk, having a VO_{2max} < 34 mL/kg/min as measured by a submaximal fitness test), not currently taking hormone replacement therapy, not a current smoker or excessive alcohol drinker (no more than two alcoholic drinks/d), a body mass index (BMI) of 22-40 kg/m^2, not previously diagnosed with cancer, not currently participating in a weight loss program and having received physician approval for exercise participation.

2.2 Intervention

Women were randomized to either 150 min/wk (MODERATE) or 300 min/wk (HIGH) of aerobic exercise. All women were instructed to exercise 5 d/wk reaching 65%-75% of heart rate reserve during 30 min/session or 60 min/session. Exercise sessions were supervised on at least 3 d/wk by certified exercise trainers at recreational facilities in Calgary and Edmonton. The exercise intervention included a 12-week ramp-up period, during which the intensity, volume, and frequency of exercise were gradually increased. Women could choose to complete any type of aerobic exercise (eg, running, walking, and cycling). The adherence to the intervention was monitored by weekly exercise logs that were completed by the participants and verified by the trainers. These logs included information on the exercise time spent in the prescribed heart rate zones and the rate of perceived exertion (Borg scale, 6-20). Subsequently, there was no intervention during the 12-month follow-up period.

2.3 Outcomes

2.3.1 Assessment of bone mineral density and bone mineral content

Total bone mineral density (BMD) and bone mineral content (BMC) were measured at baseline, 12 and 24 months by whole body dual-energy X-ray absorptiometry (DXA). Scans were taken with a Hologic Discovery A DXA system in Calgary and a General Electric Lunar iDXA in Edmonton. The DXA scanner was calibrated every day before use. Staff members were blinded to the randomization groups. Scanning instructions and procedures were standardized for all women. The analysis of the scans was done using the same protocol in Calgary and in Edmonton.

2.3.2 Covariate measures

Baseline characteristics, which include information on medical, menstrual, and reproductive history, marital status, education, employment, and history of vitamin, medication, and exogenous hormone use, were measured with a Baseline Health Questionnaire (BHQ). Osteoporosis medication use was derived from self-reported (yes/no) information captured with the BHQ and was used as a crude indicator of osteoporosis diagnosis. Diet during the past year was measured at baseline and at 12 and 24 months with the Canadian Diet History Questionnaire[19] that was originally developed by the US National Cancer Institute.

2.4 Statistical analysis

For our primary analysis, linear regression models were used to estimate the mean differences in total bone mineral density (g/cm^2) and bone mineral content (g) between treatment arms at 12 months (end of the study) and at 24 months (follow-up) after adjusting for baseline outcome values in accordance with an intent-to-treat analysis. We re-examined these results after adjusting for baseline covariates that could influence these variables.[20] These included the following: age (years), years since menopause (years), body fat (%), ethnicity (%), estrogen levels (pg/mL), presence of osteoporosis (yes/no), osteoporosis medication use (yes/no), and intake of calcium or vitamin D supplementation (yes/no). Assumptions of normality and homogeneity were assessed by examining quantile-quantile plots and histograms of the residuals, plots of the residuals vs the fitted values, and plots of the residuals vs the predictor variables. The assumption of linearity was examined through the inclusion of polynomial terms into the regression analysis. The presence of influential observations was assessed using Cook's distance. Sensitivity analyses were conducted to determine whether the results were robust to the removal of influential observations if present. In all analyses, we found no gross violations of the assumption of normality or homogeneity and all results were robust to the removal of the few potentially influential points that were identified using Cook's D (results not shown). Therefore, no transformation of the data was needed for these analyses.

We examined potential effect modification for the association between years since menopause, percent body fat, osteoporosis medication use (yes/no), vitamin D, or calcium supplementation use (yes/no) with bone mineral density and bone mineral content, given their dual effects on bone.[20]

As an exploratory analysis, a per-protocol analysis was conducted whereby women who did not adhere to at least 90% of the exercise prescription were excluded. Including the 12-week ramp-up period, being 90% adherent to the intervention corresponded to completing an average of 238.5 and 120.7 minutes of physical activity per week over 12 months for those randomized to the HIGH and MODERATE dose arms, respectively.

In an additional exploratory analysis, we examined the association between the average amount of time spent doing impact exercises and bone mineral density. We classified activities into two categories: impact vs non-impact exercises. We classified impact exercises as those where the body touches the ground and generates a gravitational load.[21] The following exercises were classified as impact exercises: running, walking, hiking, dancing, rope skipping, stair climbing, trampoline jumping, snow-shoeing, as well as playing basketball, badminton, tennis, racquetball, or participating in a group fitness class. Examples of exercises classified as being non-impact included cycling, rowing, aquafit classes, swimming, cross-country skiing, or the use of the elliptical or rope machine. We estimated the average amount of time spent doing impact exercises every week for each participant.

Analyses were conducted in STATA (version 15.1; StataCorp LLC), and the data were cleaned in R Studio (version 1.1.447). Statistical significance was set at $P < 0.05$.

3 RESULTS

Of the 400 women randomized at baseline, 379 and 330 participants had complete outcome assessments at 12 and 24 months, respectively (Figure 1). There were no differences in baseline characteristics between treatment arms except for ethnicity, calcium supplementation, and multivitamin use. Women in the MODERATE group had a greater percentage of multivitamin use, calcium and vitamin D supplementation, and a higher proportion of Caucasian women (Table 1). Women were, on average, 58 years of age, mainly Caucasian and overweight with a median BMI of 28 kg/m^2. Of the 379 women included in this analysis, 25 and 32 women had a diagnosis of osteoporosis in the HIGH and MODERATE dose groups, respectively, at baseline. No serious harmful events were reported during the intervention.[22]

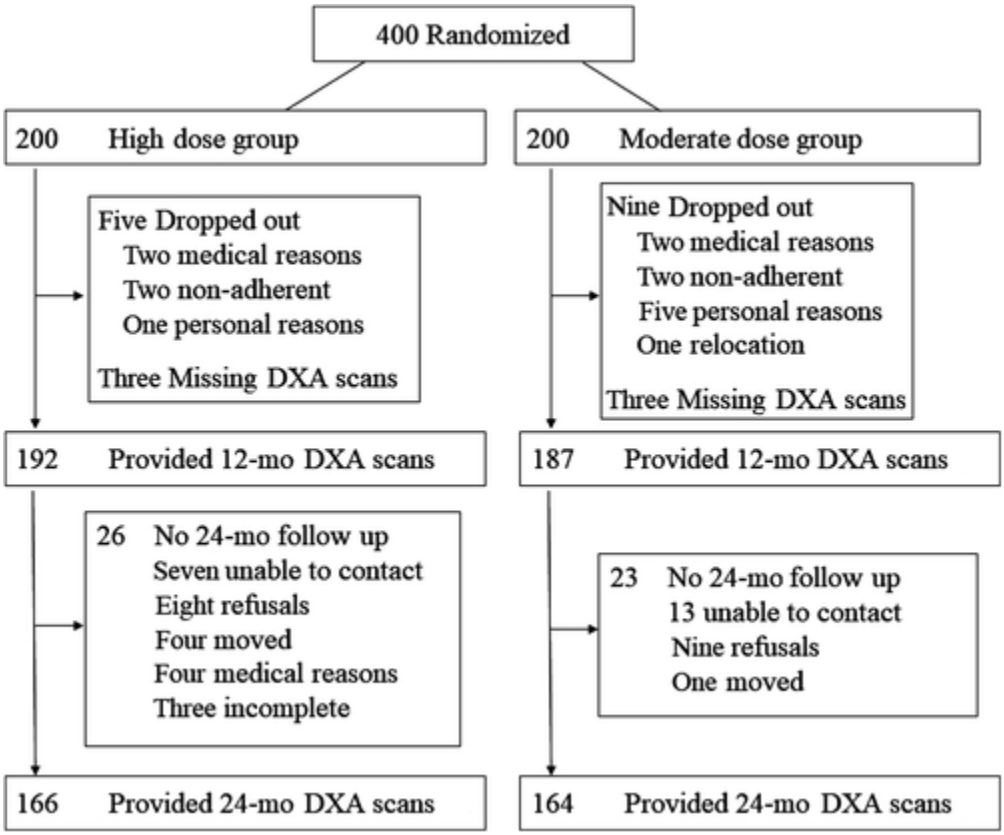

Figure 1. Participant flow diagram for the BETA Trial (0-12 mo) and the 12-mo follow-up study (12-24 mo), Alberta, Canada, 2010-2014

In the intention to treat analysis, mean bone mineral density among women randomized to the HIGH dose group was estimated to be 0.006 g/cm^2 (95% CI: 0.001-0.010) higher than that of women randomized to the MODERATE dose group at 12 months after adjusting for baseline outcomes (P = 0.02; Table 2). At 24 months, bone mineral density for the HIGH group was estimated to be 0.007 g/cm^2 (0.001-0.013) higher than the MODERATE dose group after adjusting for baseline outcomes (P = 0.02; Table 2). No significant differences between groups were found for bone mineral content (BMC) at 12 months (P = 0.87) or at 24 months (P = 0.96) after adjusting for baseline values (Table 2).

Table 1. Baseline covariates for the participants randomized to the HIGH- and MODERATE-dose groups in the Breast Cancer and Exercise Trial in Alberta (BETA), Alberta, Canada, 2010-2014 (n = 379)

Baseline characteristics	HIGH-dose group (n = 192)	MODERATE-dose group (n = 187)
Age (y)	58.5 [55.7, 62.3]	58 [56, 62.7]
Weight (kg)	74.8 [67.1, 86.3]	76 [66.4, 87]
Height (m)	1.63 [1.59, 1.66]	1.61 [1.58, 1.66]
Body mass index (kg/m^2)	28.4 [25.3, 31.8]	28.75 [26, 32.9]
Age at menopause (y)	50 [47, 52]	50 [48, 52]
Years post-menopausal (y)	8.2 [4.7, 14.0]	8.0 [4.5, 13.4]
Ethnicity		
Caucasian; N (%)	164 (85.4)	173 (92.5)
Other; N (%)	28 (14.6)	14 (7.5)
DXA measurements		
Body fat (kg)	29.7 [23.8, 36.8]	29.8 [24.3, 37.7]
Lean mass (kg)	43.7 [39.8, 47.9]	43.5 [39.5, 47.6]
Total BMC (g)	2142 [1957, 2411]	2111.00 [1890, 2412]
Total Bone Area (cm^2)	2022 [1898, 2122]	1973.6 [1869, 2114]
Total BMD (g/cm^2)	1.06 [1.01, 1.13]	1.08 [1.00, 1.13]
Osteoporosis; N (%)	25 (13.0)	32 (17.1)
Estrogens		
Estrone (pg/mL)	36.9 [30.6, 43.7]	39 [30.9, 47.5]
Estradiol (pg/mL)	9.3 [7.2, 12.3]	9.7 [7.6, 12.9]
Calcium supplement; N (%)	82 (42.7)	100 (53.5)
Vitamin D supplement; N (%)	121 (63.0)	121 (64.7)
Multivitamin supplement; N (%)	66 (34.4)	82 (43.9)
Osteoporosis medication; N (%)	15 (7.5)	22 (11)

Note: Values reported as median [IQR] and N (%) for continuous and categorical variables, respectively.
Abbreviations: BMC, Bone mineral content; BMD, Bone mineral density; DXA, dual-energy X-ray absorptiometry.

We previously reported the changes in body fat mass (kg), lean mass (kg), and VO_{2max} between groups following these exercise interventions.[22] Briefly, the mean reductions in total fat mass were significantly larger in the HIGH compared with the MODERATE dose group (least-squares mean difference, −0.96 kg, 95% CI: −1.71 to −0.22; $P = 0.01$). Lean mass was also 0.31 kg (95% CI: −0.05 to 0.68) higher at 12 months in the HIGH compared to the MODERATE dose group; however, this difference was not statistically significant ($P = 0.09$). Lastly, greater increases in VO_{2max} were noted in the HIGH vs MODERATE groups (5.09 vs 3.09 L/kg min; $P = 0.05$).[22]

Based on the per-protocol analysis (n = 211), the magnitude of the estimated effect for bone mineral density among women whose adherence to the prescribed exercise intervention was ≥90% was similar at 12 months compared to what was observed in the intent-to-treat analysis, and at 24 months, women among the HIGH dose group had higher bone mineral density than women in the MODERATE dose group; however, this difference was not statistically significant. Furthermore, results remained unchanged for bone mineral content, with no significant differences between groups at 12 and 24 months (results not shown). We have previously reported adherence data during BETA, finding relatively high exercise adherence with a total program adherence of 84.5% in the MODERATE group and 75.2% in the HIGH group.[23]

Table 2. Mean difference in bone mineral density (g/cm^2) and bone mineral content (g) between HIGH- and MODERATE-dose groups at 12 mo and at 24 mo after adjusting for baseline values among participants in BETA, Alberta, Canada, 2010-2014

	12 mo							24 mo				
	N	Baseline Mean (SD)	12-mo Mean (SD)	Mean Difference at 12 mo (95% IC)[a]	*P*-value[b]	Adherence N[c]	Adherence Mean min/wk[d]	N	Baseline Mean (SD)	24-mo Mean (SD)	Mean Difference at 24 mo (95% IC)[e]	*P*-value[b]
BMD (g/cm^2)												
High	192	1.075 (0.098)	1.064 (0.099)	0.006 (0.001 to 0.010)	0.02	89	238.5	166	1.076 (0.096)	1.064 (0.101)	0.007 (0.001 to 0.013)	0.02
Moderate	187	1.073 (0.098)	1.057 (0.101)			122	120.7	164	1.073 (0.099)	1.053 (0.106)		
BMC (g)												
High	192	2198.24 (347.99)	2185.47 (367.27)	−1.26 (−17.24 to 14.72)	0.87			166	2199.06 (370.01)	2168.03 (361.93)	0.43 (−18.29 to 19.15)	0.96
Moderate	187	2168.33 (387.92)	2158.32 (374.26)					164	2175.66 (397.36)	2145.02 (397.78)		

Abbreviations: BMC, bone mineral content; BMD, Bone mineral density; CI, Confidence interval; N, number of women completing measures at baseline and 12 and 24 mo; SD, standard deviation.

[a] Mean difference at 12 mo between groups adjusted for baseline. The reference value is the MODERATE-dose group.

[b] *P*-value refers to the statistical significance between arms.

[c] N refers to the number of women that was adherence to at least 90% of the exercise prescription.

[d] Mean minutes per week of exercise completed for women in the study. This average corresponds with a 90% adherence to the exercise prescription. Data are adapted from Stone et al.[23]

[e] Mean difference at 24 mo between groups adjusted for baseline. The reference value is the MODERATE-dose group.

When testing for effect modification, we found that the use of osteoporosis medication moderated the association between exercise dose and bone mineral density, indicating that the effects of exercise dose on bone mineral density were significantly greater among women randomized to the HIGH dose group who were not using osteoporosis medication (0.008 g/cm^2, 95% IC: 0.003-0.012; $P = 0.03$). As a result of these findings, we excluded women taking osteoporosis medication from the full model (n = 35). Results were not different at the end of the intervention (results not shown), but they were no longer statistically significant at the end of follow-up (−0.006 g/cm^2, 95% CI: −0.000 to 0.012; $P = 0.08$) when compared to our intent-to-treat results. No statistically significant interactions were found with elapsed time since menopause, body fat (%) or vitamin D and calcium supplementation for bone mineral density (Table S1). Regarding bone mineral content, effect modification was not found for any of the potential moderators (Table S1).

In an exploratory analysis, we examined the association between bone mineral density and the average amount of min/wk that the women spent doing impact exercises. A total of 77 341 sessions were recorded, of which 839 (1.1%) were missing data on the type of activity performed by the women. We observed that individuals who completed an average of >85.4 min/wk of impact exercise over the course of a year had significantly higher mean levels of bone mineral density at 12 months (0.006 g/cm^2, 95% CI: 0.006-0.012; $P = 0.03$) compared to women who did <43 min/wk of impact exercise (Table S2).

4 DISCUSSION

To our knowledge, this trial is the first to investigate the effects of prescribing different doses of exercise on total bone mineral density and bone mineral content in post-menopausal women during a 12-month intervention and at 24-month follow-up. In this 12-month intervention, inactive post-menopausal women randomized to a HIGH dose group have statistically significant higher bone mineral density compared to the MODERATE dose group at 12 months. This difference between groups remained 1 year after the end of the intervention. In contrast, we did not find significant differences between groups for bone mineral content. Therefore, completing a greater volume of exercise may help prevent some of the natural age-related decreases in bone mineral density, and these benefits may remain once the intervention concludes. Lastly, completing a higher volume of impact exercises led to a smaller decrease in bone mineral density, thus supporting our second hypothesis.

The effects of exercise on bone health in post-menopausal women have been explored in several studies[24]; however, results remain inconsistent since not all types of exercises have shown positive effects on bone mineral density.[25, 26] The majority of studies have reported the effects of exercise on specific bone regions, such as lumbar spine, femoral neck, or total hip, given the clinical relevance of these sites in the prevention of fracture risk.[27-30] Other studies, like ours, have reported the effects of exercise on whole body bone mineral density.[31-34] A comparable study is the Physical Activity for Total Health study (PATH)[35] Trial, which randomized 173 post-menopausal women to a year-long aerobic exercise intervention or a stretching control group. This study reported a non-significant difference in total bone mineral density between the control and the exercise group after the intervention.[35] Consistent with our results, some studies did not find an increase in total bone mineral density in post-menopausal women after a

moderate-intensity aerobic exercise intervention.[26, 36] In our study, we found a decrease in total bone mineral density, and one possible explanation could be related to the amount of mechanical loading and muscle tension that is needed to increase bone mass.[11] The majority of women in this study chose to walk,[22] which has been shown to be an insufficiently strong stimulus to help preserve bone mineral density.[15, 24] Impact exercise and resistance training have been shown to be very effective modes of exerting a mechanical load[37, 38]; hence, they may lead to greater improvements in bone mineral density. Indeed, our exploratory analysis revealed that greater improvements in bone mineral density were seen in women who reported completing a greater amount of impact exercises. These results are consistent with previous studies that found benefits of impact exercises on bone health.[14, 37]

We noted that the effects of exercise dose on bone mineral density were significantly greater among women who were not using osteoporosis medication. Therefore, women with established osteoporosis did not show an added benefit of greater exercise volume on bone mineral density. However, these results do suggest that exercise could potentially be used as a non-pharmacological strategy to prevent post-menopausal bone loss and delay the use of osteoporosis drugs. However, these results should be interpreted with caution as there were a limited number of women taking osteoporosis medication in our intervention. Although non-significant, our results may suggest that elapsed time since menopause may modify the association between exercise and bone mineral density, where the effects of exercise dose on bone mineral density were greater in women with a longer elapsed time since menopause. Bone mineral density loss during menopause is not linear, since it decreases rapidly during the first years of menopause and then attenuates.[39] It is also possible that women who had lower baseline bone mineral density may have less loss due to an inability to lose a large amount of BMD over the course of the intervention. Therefore, it is possible that our exercise interventions were unable to prevent some of this rapid decrease in bone mineral density seen during and shortly after menopause, which corroborates previous findings reported by the PATH Trial.[35]

Bone mineral content is also an indicator of fracture risk and osteoporosis[3]; however, most of the studies conducted in post-menopausal women have focused on reporting bone mineral density measurements.[24] In the present study, we found that both BMD and BMC decreased at 12 and 24 months for both groups, whereas there were no significant differences between the MODERATE and the HIGH group for bone mineral content. Since BMD is a ratio between BMC and bone size, variations in BMD could be attributable to variations in both of these components. Future studies should report both BMC and BMD measurements to allow for further comparisons between these measurements in various populations.

The main limitation of this study was that regional scans for bone mineral density or bone mineral content were not performed since bone measurements were not a primary outcome of BETA. Therefore, we are unable to assess the effects of these exercise interventions on the total hip or the femoral neck, which are of clinical relevance for predicting the risk of fractures. Furthermore, DXA alone cannot capture all the benefits that exercise may cause in post-menopausal bone health, such that other methods like peripheral quantitative computed tomography (pQCT) could be used to better understand the effects of exercise on bone health.

In conclusion, our results suggest that prescribing a higher dose of exercise, especially impact exercise, may attenuate some of the natural age-related declines in total bone mineral density in post-menopausal women and that these benefits may remain once the intervention concludes. Despite these findings, it is important to recognize that declines in bone mineral density and bone mineral content occurred in all women at 12 and at 24 months compared to baseline.

5 PERSPECTIVE

There is currently little evidence on the effects of exercise volume that may be needed to improve or prevent age-related declines in bone mineral density. To our knowledge, this is the largest study to investigate the dose-response effects of exercise on total bone mineral density. Our findings suggest that post-menopausal women could delay some of the loss in total bone mineral density by performing a greater volume of aerobic exercise, especially if this exercise has a weight-bearing component. Further studies are needed to corroborate these findings, with an emphasis on regional bone mineral density and bone mineral content measurements to understand the clinical relevance of exercise dose in bone health.

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CONFLICT OF INTERESTS

The authors of this document declare that they have no conflict of interest derived from the outcomes of this study.

AUTHOR CONTRIBUTIONS

CMF and KSC were involved in the conception and design of the study and obtained study funding. DJB conducted the data processing. PGE, JM, and DJB conducted the statistical analysis and interpreted the data. PGE drafted the manuscript. All authors critically revised the manuscript for intellectual content, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work at appropriately investigated and resolved.

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